Short-term neurological improvement in neonates with hypoxic-ischemic encephalopathy predicts neurodevelopmental outcome at 18–24 months

Grass, Beate ; Scheidegger, Simone ; Latal, Beatrice ; Hagmann, Cornelia ; Held, Ulrike ; Brotschi, Barbara

Abstract: Objectives To evaluate the association of short-term neurological improvement until day of life 4 in neonates with hypoxic-ischemic encephalopathy (HIE) receiving therapeutic hypothermia (TH) with neurodevelopmental outcome at 18-24 months. Methods This is a retrospective analysis of prospectively collected data of 174 neonates with HIE registered in the Swiss National Asphyxia and Cooling Register between 2011 and 2013. TH was initiated according to national guidelines, and Sarnat staging was performed daily. Short-term neurological improvement was defined if Sarnat stage improved from admission until day 4 of life. Standardized neurodevelopmental assessments were performed at 18-24 months. Unfavorable outcome was defined as death before 2 years of age or severe or moderate disability at follow-up. Results One hundred and sixty-four of 174 neonates (94%) received TH, of those 30 (18%) died in the neonatal period (no late mortality). Eighty-one percent of the survivors (109/134) were seen at 18-24 months. Of the 164 cooled neonates, 62% had a short-term neurological improvement, and the Sarnat score remained unchanged in 33%. Short-term neurological improvement was associated with an odds ratio (OR) of 0.118 [95% confidence interval (CI) 0.051-0.271] for an unfavorable outcome at 18-24 months. Conclusion Short-term neurological improvement predicts neurodevelopmental outcome at 18-24 months in the era of TH. Clinical examination must be part of a comprehensive evaluation for prognostication in HIE.

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Beate Grass*, Simone Scheidegger, Beatrice Latal, Cornelia Hagmann, Ulrike Held, Barbara Brotschi and National Asphyxia and Cooling Register Group and Follow-up Group

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Conclusion: Short-term neurological improvement predicts neurodevelopmental outcome at 18–24 months in the era of TH. Clinical examination must be part of a comprehensive evaluation for prognostication in HIE.

Keywords: hypoxic-ischemic encephalopathy; neurodevelopmental outcome; prognostication.

***Corresponding author: Beate Grass,** MD, Department of Pediatric and Neonatal Intensive Care, University Children's Hospital Zurich, Steinwiesstr. 75, 8032 Zurich, Switzerland, Phone: +41 44 266 3765, Fax: +41 44 266 7168, E-mail: beate.grass@kispi.uzh.ch. https://orcid.org/0000-0002-4965-2814

Simone Scheidegger, Cornelia Hagmann and Barbara Brotschi: Department of Pediatric and Neonatal Intensive Care, University Children's Hospital Zurich, Zurich, Switzerland

Beatrice Latal: Child Development Center, University Children's Hospital Zurich, Zurich, Switzerland

Ulrike Held: Department of Biostatistics, Epidemiology, Biostatistics and Prevention Institute, University of Zurich, Zurich, Switzerland

Introduction

Despite therapeutic hypothermia (TH), up to 50% of neonates with moderate or severe hypoxic-ischemic encephalopathy (HIE) die or suffer from severe neurodevelopmental impairment (NDI) [1, 2]. Prediction of expected neurodevelopmental outcome is crucial during the first few days after birth. Different tools to estimate long-term prognosis have been studied in the literature and are used for counseling parents (amplitude-integrated electroencephalography, conventional electroencephalography, magnetic resonance imaging, cranial ultrasound, near-infrared spectroscopy, serum biomarkers, placenta histology). The predictive value of these newer imaging and electrophysiological tools is limited [3, 4]. Additionally, repeated clinical examination as one of the earliest tools to evaluate encephalopathy over the first days of life may help to estimate prognosis [3, 5, 6].

In 1976, Sarnat and Sarnat evaluated 21 neonates with perinatal asphyxia and encephalopathy using a standardized neurological score [7]. In the original Sarnat publication [7], those neonates with persistent Sarnat stage 3 until day of life 5 had an unfavorable outcome.

Almost all randomized controlled trials analyzing the efficacy of TH for neonates with HIE used Sarnat staging as inclusion criteria [1, 2, 8]. However, there is some uncertainty about the significance of clinical examination during and after TH and its predictive value [5]. Bonifacio et al. concluded that TH has altered the predictive value of severity of encephalopathy on admission [3]. The predictive ability of the clinical examination shortly after rewarming has also changed as neonates with TH and persistent moderate encephalopathy on day 4 still had better

neurodevelopmental outcomes compared to neonates without TH [3, 5, 6]. After TH has become the standard of care, the value of repeated clinical examinations to assess the evolution of encephalopathy in TH and its impact on neurodevelopmental outcomes after TH has not been reported yet.

The aim of this study was to examine the association of short-term neurological improvement between admission and day 4 of life with neurodevelopmental outcome at 18–24 months of age in neonates with HIE receiving TH.

Materials and methods

This is a retrospective analysis of prospectively collected data of a multicenter cohort study including 174 neonates (≥35 0/7 weeks of gestational age) with HIE registered in the Swiss National Asphyxia and Cooling Register between 2011 and 2013. TH was initiated within 6 h of birth at 33.0–34.0 °C core temperature (whole-body cooling with ice gel packs or servo coolers) and continued for 72 h according to the national guidelines for neonates with HIE published previously [9, 10]. Maternal and neonatal demographics, perinatal data, clinical presentation and follow-up data were collected from the entries in the Swiss National Asphyxia and Cooling Register and amended by review of the maternal and neonatal charts as appropriate.

Data collection, evaluation and publication for this study were approved by the Swiss Ethical Committee and the Swiss Federal Commission for Privacy Protection in Medical Research. The study is registered in ClinicalTrials.gov (NCT02800018).

All neonates had clinical examinations according to Sarnat staging performed by a senior neonatal consultant on admission and within 24, 48, 72 and 96 h of life, respectively [7]. Neurological short-term improvement was defined if Sarnat stage improved between admission and day 4 of life or if the Sarnat score remained 1 throughout [11].

Neurodevelopmental follow-up assessments were performed by pediatric neurologists or developmental pediatricians at 18–24 months of age. The assessment consisted of a clinical examination, a structured neurological assessment (including hearing and vision) and a developmental assessment using the Bayley Scales of Infant Development, Second Edition (Bayley-2) (n = 20) [12], the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-3) (n = 83) [13] or the Griffith Scale (n = 6) [14] according to the follow-up center's guidelines. In order to compare the different versions of the Bayley Scales, conversion equations from regression analysis were applied for a conversion of Bayley-2 to Bayley-3 according to Jary et al. [15]. The Griffith Score was not converted, as suggested by Cirelli et al. [16]. Cerebral palsy [17] was graded according to the Gross Motor Function Classification System (GMFCS) of Palisano et al. for children aged ≤2 years [18].

Primary outcome

Outcome was defined according to previously published randomized controlled trials, investigating neurodevelopmental outcome at 18–24 months [1, 2, 19].

Unfavorable outcome was defined as either:

(i) All deaths before 2 years of age.
(ii) Severe disability, which was defined as any of the following: a cognitive or language Bayley-3 score more than 2 standard deviation (SD) below the mean score (i.e. <70), a GMFCS grade of level 3–5, hearing impairment requiring hearing aids or blindness.
(iii) Moderate disability, which was defined as a cognitive or language Bayley-3 score of 1–2 SD below the mean score (i.e. 70–84) in addition to one or more of the following: a GMFCS grade of level 2, hearing impairment with no amplification or a persistent seizure disorder.

Favorable outcome was defined as either:

(iv) Mild disability, which was defined as a cognitive or language Bayley-3 score of 70–84 alone, or a cognitive or language Bayley-3 score ≥85 and a GMFCS level 1 or 2, seizure disorder (without anti-epileptic medication) or hearing deficit with the ability to follow commands without amplification.
(v) Absence of any of the above.

Statistical methods

We investigated the dichotomous outcome (unfavorable vs. favorable) as well as single outcome components. Descriptive statistics included mean and SD for the continuous variables, as well as number and percentage of total for the categorical variables. In a tabulation of descriptive statistics within strata of neurological improvement, exploratory P-values were calculated; these were from chi-square (χ^2) tests, Wilcoxon tests or *t*-tests, if the risk factors were categorical, ordinal or continuous, respectively.

The binary outcome "unfavorable outcome" was addressed with logistic regression, and odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were estimated. To quantify the association with additional risk factors, multiple logistic regression models were used. A subgroup analysis of the prevalence of favorable outcome stratified by Sarnat stage on admission was performed using one-sample proportion tests with continuity correction.

Results are reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [20]. All analyses were conducted using R [21].

Results

Study population: neonatal data and neurodevelopmental assessment at 18–24 months

Data of 174 neonates with HIE were recorded in the Swiss National Asphyxia and Cooling Register between 2011 and 2013. A flowchart of the study population is provided in Figure 1. Ten neonates (6%) with Sarnat stage 1 on admission received normothermia and did not undergo follow-up visits. These neonates were excluded from further

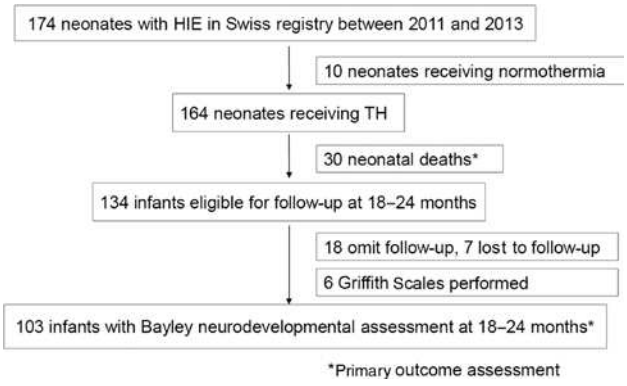

Figure 1: Flowchart of the study population.

analysis. Of the 164 included neonates, 158 (96%) were scored as Sarnat 2 (126/164; 77%) and Sarnat 3 (32/164; 19%), and the remaining six (4%) were cooled despite being scored Sarnat 1 on admission, based on the clinical judgment of the attending neonatologist. Demographic neonatal data are given in Table 1. Fifty-five infants (33%) were not available for follow-up: 30 (18%) neonatal deaths (13 neonates with Sarnat stage 2, 17 neonates with Sarnat stage 3 on admission), 18 (11%) infants did not attend follow-up (parental refusal, n = 15; moving countries, n = 3) and seven (4%) infants were lost to follow-up.

The primary outcome at 18–24 months could be assessed in 133 of 164 infants (81%). Thirty neonatal deaths occurred and 103 infants were assessed with Bayley-2 (20/103; 19%) or Bayley-3 (83/103; 81%) at 18–24 months. The information on the 103 infants who had neurodevelopmental outcome assessment is presented in Table 2.

Short-term neurological improvement and its association with neurodevelopmental outcome at 18–24 months

Of the 164 cooled neonates, 62% (102/164) had a short-term neurological improvement on the Sarnat score during the first 4 days of life. The Sarnat score remained unchanged in 33% (54/164) of neonates. No neonate showed persistent worsening encephalopathy during the first 4 days of life. In eight (5%) neonates, only one Sarnat score was assessed during the first 4 days of life; thus, these neonates were excluded from further analysis. The characteristics of the two groups (short-term neurological improvement yes/no) are given in Table 3.

The association of short-term neurological improvement until day of life 4 with neurodevelopmental outcome at 18–24 months is shown in Table 3.

Table 1: Descriptive statistics for demographic and clinical variables, measured at birth and until discharge from NICU.

Demographic variable	Overall
Included neonates, n	164
Male sex, n (%)	95 (57.9)
Outborn, n (%)	133 (81.1)
Gestational age, mean (SD), days	275 (13), i.e. 39 + 2 weeks
Birth weight, mean (SD), g	3306 (560)
Sentinel event[a], n (%)	60 (36.6)
Cesarean section[b], n (%)	87 (53.0)
SES score[c], mean (SD)	5.6 (2.2)
Maternal age, mean (SD), years	31.7 (5.1)
Head circumference at birth, mean (SD), cm	34.4 (1.7)
Apgar 1 min, median (IQR)	1 (1.00, 2.00)
Apgar 5 min, median (IQR)	3 (2.00, 5.00)
Apgar 10 min, median (IQR)	5 (3.00, 6.00)
Prolonged resuscitation > 10 min, n (%)	94 (57.3)
Arterial cord pH, mean (SD)	6.91 (0.23)
Lowest pH[d], mean (SD)	6.87 (0.18)
Lowest base excess[d], mean (SD)	−19.2 (6.3)
Lowest bicarbonate[d], mean (SD)	12.9 (4.6)
Hypoglycemia[e], n (%)	30 (18.3)
Seizures, n (%)	56 (34.1)
Sarnat stage on admission, n (%)	
Sarnat 1	6 (3.7)
Sarnat 2	126 (76.8)
Sarnat 3	32 (19.5)
Sarnat score improvement between DOL 1 and 4, n (%)	
No	54 (32.9)
Yes	102 (62.2)
NA	8 (4.9)
Neonatal deaths, n (%)	30 (18.3)

DOL, day of life; NA, not available; SD, standard deviation. [a]Includes placental abruption, uterine rupture, maternal hemorrhage/shock, cord prolapse and amniotic embolism. [b]Includes planned, unplanned and emergency cesarean section. [c]Maternal and paternal socioeconomic score (SES), divided by two. SES was calculated according to the recommendations of Largo et al. [22]: SES of the mother plus SES of the father or one of them doubled if one was unknown. [d]Values from arterial/venous/capillary samples within the first 60 min of life. [e]At least one single blood glucose measurement of <2.5 mmol/L.

Short-term neurological improvement was associated with a lower likelihood of an unfavorable outcome at 18–24 months (OR 0.118, 95% CI 0.051–0.271, P-value < 0.001).

Four out of four neonates (100%, 95% CI 40%–100%) with Sarnat stage 1 on admission had a favorable neurodevelopmental outcome. Seventy-two out of 98 neonates (73%) with Sarnat stage 2 on admission had a favorable neurodevelopmental outcome (95% CI 63%–82%). In neonates with Sarnat stage 3 on admission, 10 out of 31

Table 2: Descriptive statistics for the outcome variables at 18–24 months for those 103 infants whose follow-up data were available.

Outcome variable	Overall
Infants with FU available, n	109, 103 included[a]
Age at FU, mean (SD), months	22.63 (3.34)
Head circumference at FU, mean (SD), cm	48.06 (1.80)
Head circumference at FU, mean (SD), z-score	−0.64 (1.45)
Cognitive Bayley-3 score, mean (SD)	106.57 (15.07)
Language Bayley-3 score, mean (SD)	98.79 (17.49)
Motor Bayley-3 score, mean (SD)	98.31 (12.12)
Cerebral palsy, n (%)	6 (5.5)
Seizures, n (%)	3 (2.8)
Severe visual impairment, n (%)	2 (1.8)
Severe hearing impairment, n (%)	2 (1.8)
Outcome category, n (%)	
Normal	73 (67.0)
Mild NDI	13 (11.9)
Moderate NDI	5 (4.6)
Severe NDI	12 (11.0)
Death (after NICU discharge)	0 (0.0)
NA[a]	6 (5.5)
Unfavorable outcome[b], n (%)	
No	86 (78.9)
Yes	17 (15.6)
NA[a]	6 (5.5)

FU, follow-up; NA, not available; NDI, neurodevelopmental impairment; SD, standard deviation. [a]No standardized follow-up assessment available that could have been transformed into Bayley-3 scoring (Griffith Scales performed). [b]Unfavorable outcome: moderate or severe disability at FU assessment; death reported separately as no deaths occurred after NICU discharge.

neonates (32%) had a favorable neurodevelopmental outcome (95% CI 17%–51%).

If Sarnat stage improvement was taken as a short-term marker to predict favorable neurodevelopmental outcome at 18–24 months, the sensitivity and specificity are important quality criteria for this diagnostic test [23]. These parameters with 95% CIs are given in Table 4.

Discussion

Outcome prediction in neonates with HIE in the era of TH might be different than in the pre-cooling era. To date, no single clinical tool exists to reliably predict neurodevelopmental outcome in HIE [3, 4]. HIE is a clinical diagnosis characterized by a disorder of neurological function occurring after perinatal asphyxia. Repeated clinical assessment of the severity of encephalopathy is an easily accessible, inexpensive and non-invasive bedside examination.

We investigated the predictive value of short-term neurological improvement during the first 4 days of life and neurodevelopmental outcome at 18–24 months in a multicenter cohort study including 164 cooled neonates with HIE registered in the Swiss National Asphyxia and Cooling Register. Our data provide strong evidence for an association between short-term neurological improvement until day of life 4 and a favorable outcome at 18–24 months of age. We showed that if there was a short-term neurological improvement on the Sarnat score between admission and day of life 4, there was a very low risk of an unfavorable outcome at 18–24 months of age. In the prediction model, the sensitivity of a favorable outcome after short-term neurological improvement was 63%. Moreover, those without early neurological improvement were unlikely to have a favorable outcome at 18–24 months, with a specificity of 83%.

In the original Sarnat publication [7], those neonates with persistent Sarnat stage 3 until day of life 5 had an unfavorable outcome, compared to those who normalized their neurologic examination over time. Previous studies investigated the influence of TH on the prognostic value of clinical evaluation in HIE [5, 6]. Data of these studies confirmed that the evolution of encephalopathy over the first days of life predicts neurodevelopmental outcome in cooled and non-cooled neonates [5, 6].

A secondary analysis of the National Institute of Child Health and Human Development (NICHD) trial on TH in HIE [6] recommended the use of the Sarnat score at less than 6 h of age for patient selection for TH and the Sarnat score at the end of TH as a predictor of neurodevelopmental outcome at 18 months. Neonates receiving TH showed an earlier improvement of encephalopathy in the daily assessments compared to normothermic neonates. Similarly, re-analyzed data from the Cool Cap trial [24] including TH and normothermia confirmed that less severe encephalopathy, more improvement in encephalopathy and treatment with TH itself were associated with better neurodevelopmental outcome at 18 months [5]. However, they did not have daily Sarnat scores available for their analysis. Shankaran et al. showed that the change in Sarnat stage in serial examinations better predicted outcome than the Sarnat score on admission in a cohort of normothermic and cooled neonates with HIE [6]. The studies by Shankaran et al. and Gunn et al. conclude that the improvement of encephalopathy during TH is associated with a favorable neurodevelopmental outcome whereas the deterioration of encephalopathy predicts an unfavorable outcome [5, 6].

Table 3: Neurological improvement during the first 4 days of life and its association with neonatal characteristics and neurodevelopmental outcome at 18–24 months.

Variables	No neurological improvement	Neurological improvement	P-value
Neonatal variables			
n	54	102	
Male sex, n (%)	28 (51.9)	65 (63.7)	0.205
Outborn, n (%)	48 (88.9)	78 (76.5)	0.097
Gestational age, mean (SD), days	274.22 (13.92)	275.69 (11.93)	0.493
Birth weight, mean (SD), g	3243.89 (601.41)	3338.85 (554.74)	0.325
Head circumference at birth, mean (SD), cm	33.92 (1.75)	34.66 (1.64)	0.021
Sentinel event[a], n (%)	21 (38.9)	37 (36.3)	0.883
Caesarean section[b], n (%)	32 (59.3)	51 (50.0)	0.35
SES score[c], mean (SD)	5.33 (1.34)	5.69 (2.49)	0.403
Maternal age, mean (SD), years	31.87 (5.07)	31.49 (5.15)	0.67
Apgar 1 min, median (IQR)	1.00 (0.00, 2.00)	1.00 (1.00, 2.00)	0.472
Apgar 5 min, median (IQR)	3.00 (2.00, 5.00)	3.00 (3.00, 5.00)	0.202
Apgar 10 min, median (IQR)	4.00 (2.00, 6.00)	5.00 (3.00, 6.00)	0.25
Prolonged resuscitation >10 min, n (%)			0.649
No	19 (35.2)	43 (42.2)	
Yes	34 (63.0)	58 (56.9)	
NA	1 (1.9)	1 (1.0)	
Arterial cord pH, mean (SD)	6.90 (0.18)	6.92 (0.26)	0.772
Lowest pH[d], mean (SD)	6.85 (0.20)	6.89 (0.17)	0.186
Lowest base excess[d], mean (SD)	−19.78 (6.68)	−18.92 (6.08)	0.481
Lowest bicarbonate[d], mean (SD)	11.54 (4.59)	13.70 (4.53)	0.027
Sarnat score on admission, n (%)			0.023
Sarnat 1	0 (0.0)	6 (5.9)	
Sarnat 2	38 (70.4)	81 (79.4)	
Sarnat 3	16 (29.6)	15 (14.7)	
Hypoglycemia[e], n (%)	13 (24.1)	16 (15.7)	0.287
Seizures, n (%)	31 (57.4)	24 (23.5)	<0.001
Neonatal deaths, n (%)	27 (50.0)	3 (2.9)	<0.001
Follow-up variables			
Head circumference at FU, mean (SD), cm	47.92 (2.23)	48.10 (1.67)	0.705
Head circumference at FU, mean (SD), z-score	−0.74 (1.91)	−0.64 (1.34)	0.8
Cognitive Bayley-3 score >85, n (%)	15 (27.8)	72 (70.6)	<0.001
Language Bayley-3 score >85, n (%)	14 (25.9)	56 (54.9)	<0.001
Motor Bayley-3 score >85, n (%)	15 (27.8)	70 (68.6)	<0.001

Descriptive statistics of the risk factors at birth and neurodevelopmental outcome at 18–24 months, stratified by short-term improvement (i.e. Sarnat score improvement between admission and day of life 4). Descriptive statistics of these variables are displayed together with exploratory P-values from χ^2 tests (for categorical variables) as well as Wilcoxon tests (for ordinal variables) and *t*-tests (for continuous variables). If medians and interquartile ranges (IQR) are given as summary measure, the variable was considered ordinal. [a]Includes placental abruption, uterine rupture, maternal hemorrhage/shock, cord prolapse and amniotic embolism. [b]Includes planned, unplanned and emergency cesarean section. [c]Maternal and paternal socioeconomic score (SES), divided by two. SES was calculated according to the recommendations of Largo et al. [22]: SES of the mother plus SES of the father or one of them doubled if one was unknown. [d]Values from arterial/venous/capillary samples within the first 60 min of life. [e]At least one single blood glucose measurement of <2.5 mmol/L.

Our study, performed after TH has become the standard of care, while the two aforementioned studies were randomized controlled trials evaluating TH, supports their results. Sixty-two percent of the neonates in our study cohort had a short-term neurological improvement and 80% of them had a favorable outcome at 18–24 months of age. In the Cool Cap cohort, the short-term improvement of encephalopathy in the TH group was calculated to be 33% [5]. In the NICHD cohort, Shankaran et al. [6] described short-term neurological improvement in 16–44% and reported daily clinical assessment of encephalopathy. The different rate of neurological short-term improvement in these three cohorts is remarkable, considering that Sarnat scoring for grading of encephalopathy was used

Table 4: Short-term improvement measured by improvement in the Sarnat score, as a diagnostic test for favorable neurodevelopmental outcome at 18–24 months.

	Estimate	Lower 95% CI	Upper 95% CI
Sensitivity	0.64	0.49	0.77
Specificity	0.83	0.73	0.9
PPV	0.68	0.52	0.81
NPV	0.80	0.7	0.88

Evaluation of short-term neurological improvement (measured with the Sarnat score) as a diagnostic test for favorable neurodevelopmental outcome at 18–24 months. CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value.

in all three studies. Probably, this is related to a gain in experience in performing Sarnat scoring in cooled neonates or the overall improved management of cooled neonates with HIE during the last few years due to increasing experience. In contrast to other studies [5, 6], there was no worsening encephalopathy in our cohort. This might be explained by the fact that we classified neonates with the trajectory of any neurological improvement between admission and day of life 4 as improvement and did not account for intermittent worsening of encephalopathy if followed by later improvement compared to Sarnat stage on admission. Notably, those eight neonates with only one single Sarnat scoring on admission in our cohort all survived, which makes worsening encephalopathy also highly unlikely.

The clinical presentation of our study population was similar to that of previously published HIE cohorts.

There was no late mortality after discharge from the neonatal intensive care unit (NICU). Early neonatal deaths were mainly due to redirection of care if very unfavorable outcome was expected. We applied the same criteria for favorable and unfavorable outcomes as used in the randomized controlled trials on TH [1, 2]. However, in accordance with more recently published studies [19], we used Bayley-3 assessments at 18–24 months (instead of Bayley-2) as Bayley-3 is established as a standard test nowadays. We used the cut-off values for Bayley-3 to define mild/moderate/severe disability as suggested by Laptook et al. [19]. We reached a high follow-up rate of 81% (of the survivors) at the age of 18–24 months and children will further be followed-up until school age.

The generalizability of our results is limited due to the relatively small sample size. We focused on the predictive strength of clinical examinations (daily Sarnat score) with almost no missing data in the National Asphyxia and Cooling Register [10]. Therefore, the evolution of encephalopathy during TH is a valuable clinical outcome predictor in our setting. However, we did not account for the interrater reliability (between cooling centers) in Sarnat scoring. We did not include cerebral magnetic resonance imaging findings. After the implementation of the National Asphyxia and Cooling Register, cerebral magnetic resonance imaging assessment after rewarming is increasingly performed nowadays, but in no more than 62% of neonates with TH in 2011–2012 [10]. There were inconsistent data on electroencephalography recordings and anti-epileptic medication and thus this risk factor could not be analyzed. Furthermore, we were not able to collect data on inter-current illnesses between discharge from NICU and follow-up assessment. Inter-current illness including prolonged hospitalization might worsen neurodevelopmental outcome independent of HIE. Neurodevelopmental interventions to mitigate impairment also were not reported.

Clinical examination to assess encephalopathy for outcome prediction remains a meaningful, easily accessible, inexpensive and non-invasive bedside tool in the era of magnetic resonance imaging and electrographical monitoring for neonates who are treated with TH for HIE. Obviously, in high-income countries, counseling parents relies on a comprehensive evaluation of the available clinical, electrographical and neuro-imaging data. The results of our study show that a detailed and serial clinical neurological examination during TH for HIE can provide valid outcome prediction abilities. Therefore, teaching clinical neurological examination skills to younger colleagues is of highest importance to maintain the expertise of assessing neonates with encephalopathy.

Author contributions: BG and BB conceived and designed the study. BG was responsible for acquisition of data, data analysis and interpretation, search and review of literature and drafting of the manuscript. SS helped with the acquisition of data, data analysis and critical review of the manuscript. UH performed all statistical analyses of the study, interpreted the results and critically revised the manuscript. BB, BL and CH supervised the design of the study, data analysis and interpretation, search and review of literature and critical review of the manuscript. All authors have read and approved the final manuscript. All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.

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Collaborators: The National Asphyxia and Cooling Register Group: Aarau: Cantonal Hospital Aarau, Children's Clinic, Department of Neonatology (G. Zeilinger); Basel: University Children's Hospital Basel (UKBB), Department of Neonatology (S.M. Schulzke, S.Wellmann); Berne: University Hospital Berne, Department of Pediatric Intensive Care (B. Wagner, K. Daetwyler); Chur: Children's Hospital Chur, Department of Neonatology (W. Bär, B.Scharrer); Lausanne: University Hospital (CHUV), Department of Neonatology (J.-F. Tolsa, A. Truttmann, J. Schneider); Geneva: University Hospital (HUG), Division of Neonatology (R. E. Pfister); Lucerne: Children's Hospital of Lucerne, Neonatal and Pediatric Intensive Care Unit (T. M. Berger, M. Fontana); St.Gallen: Children's Hospital St. Gallen, Neonatal and Pediatric Intensive Care Unit (J. P. Micallef, I. Hoigné); Zurich: University Hospital Zurich (3), Department of Neonatology (D. Bassler, G. Natalucci, M. Adams); and University Children's Hospital Zurich, Department of Intensive Care and Neonatology (B. Frey, V. Bernet).

Follow-Up Group: Aarau: Cantonal Hospital Aarau, Children's Clinic, Department of Neuropaediatrics (A. Capone Mori, D. Kaeppeli); Basel: University of Basel Children's Hospital (UKBB), Department of Neuropaediatrics and Developmental Medicine (P. Weber, M. Brotzmann); Bellinzona: San Giovanni Hospital, Department of Paediatrics (G.P. Ramelli, B. Goeggel Simonetti); Berne: University Hospital Berne, Department of Neuropaediatrics (M. Steinlin, S. Grunt); Biel: Children's Hospital Wildermeth, Development and Paediatric Neurorehabilitation Center (R. Hassink); Chur: Children's Hospital Chur, Department of Neuropaediatrics (E. Keller, Ch. Killer); Fribourg: Cantonal Hospital Fribourg, Department of Neuropaediatrics (K. Fuhrer); Geneva: Department of Child and Adolescent, University Hospital (HUG), Division of Development and Growth (P. S. Hüppi); Lausanne: University Hospital (CHUV), Department of Child Development (M. Bickle-Graz, A. Torregossa); Lucerne: Children's Hospital of Lucerne, Department of Neuropaediatrics (T. Schmitt-Mechelke, F. Bauder); Lugano: Regional Hospital Lugano, Department of Paediatrics (V. Pezzoli); Muensterlingen: Cantonal Hospital Muensterlingen, Department of Paediatrics (B. Erkert, A. Mueller); Neuchatel: Cantonal Hospital Neuchatel, Department of Paediatrics (M. Ecoffey); St. Gallen: Children's Hospital St. Gallen, Department of Child Development (A. Lang-Dullenkopf); Winterthur: Cantonal Hospital Winterthur, Social Paediatrics Center (M. von Rhein); Zurich: University Hospital Zurich (USZ), University Children's Hospital Zurich, Child Development Center (B. Latal, G. Natalucci).

Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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